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Pyoderma gangrenosum or necrotizing fasciitis? A diagnostic conundrum. Case report and literature review



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ABSTRACT

Necrotizing fasciitis (NF) is a life-threatening, rare soft tissue infection characterized by rapidly spreading necrosis of the fascia and subcutaneous tissue, muscle, and overlying skin. Once suspected, immediate and extensive surgical debridement of necrotic tissues and appropriate systemic antibiotic coverage are necessary. On the contrary, pyoderma gangrenosum (PG) is an auto-inflammatory condition of the skin that has been associated with multiple factors including inflammatory bowel disease, arthritis, and myelodysplastic disorders. It is a non-infectious process requiring non-surgical management. Both conditions are rare in the pediatric population, and may present with significant ulceration and tissue necrosis. Lack of diagnostic clinical, histopathologic, and laboratory features make identification of these entities challenging. We present a case of pyoderma gangrenosum, initially diagnosed as cellulitis and necrotizing fasciitis, to highlight the diagnostic challenges involved in differentiating these disease entities and clinical implications of misdiagnosis or delayed diagnosis.

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Pyoderma gangrenosum (PG) is an inflammatory dermatologic condition that presents with ulceration and tissue necrosis, similar to infectious processes including necrotizing fasciitis (NF) [1,2]. Our case report highlights the diagnostic pitfalls and associated clinical implications of these disease entities and emphasizes the significance of understanding the pathogenesis, clinical features, and management of both conditions.

1. Case report

A 16-year-old female was transferred to the University of Florida (UF) hospital with a working diagnosis of necrotizing fasciitis. A brief history of her presentation indicated that she had been bitten by a cat on her left hand 2 weeks prior and was seen by her primary care doctor who administered an intramuscular injection of ceftriaxone on the right gluteal region. Within 2 days, she developed erythema, intense pain, and vesiculation at the injection site. She went to the local emergency department where she was found to be febrile with a temperature of 104°F with significant leukocytosis – white blood cell count of 30,000/mm³, and elevated inflammatory markers – C-reactive protein (CRP) of 300 mg/L. A diagnosis of cellulitis was made (Fig. 1), cultures obtained and systemic

antibiotics initiated with zosyn (piperacillin and tazobactam) and vancomycin. A surgery consultation was initiated for debridement of necrotic wound areas. One day following debridement, exaggeration of the ulcerated margins was noted and diagnosis modified to necrotizing fasciitis. Her hospitalization was complicated by systemic inflammatory response syndrome (SIRS), lobar pneumonia and septic shock requiring fluid resuscitation and vasopressors. She also had a left upper extremity deep venous thrombosis and ulceration at the site of a peripherally inserted central catheter, necessitating anticoagulation therapy. A decision was made to transfer the patient to UF hospital for hyperbaric oxygen therapy.

The patient was admitted to our pediatric intensive care unit where her wounds were managed by hyperbaric oxygen treatments, serial surgical debridement of necrotic tissue, systemic antibiotics, and negative pressure wound therapy using a vacuum assisted closure dressing. She still had intermittent fevers and her inflammatory markers and leukocytosis remained elevated. Surgical debridement resulted in remarkable expansion of wound margins (Fig. 2). All blood, urine, sputum, and tissue cultures were negative. Tissue samples sent for histopathologic diagnosis revealed erosion of the epidermis with dense and diffuse neutrophilic infiltrate in the dermis and subcutis were thought to be suggestive of an acute cellulitis and panniculitis compatible with necrotizing fasciitis (Fig. 3). Special stains for bacteria, fungi, and

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Fig. 1. Cellulitis with focal areas of bullae formation.

spirochetes including gram, periodic acid-schiff, and steiner stains respectively, were performed and were all negative. Dermatology service was consulted 1 week into her hospitalization given lack of clinical improvement despite current therapies. Further querying of the patient's mother revealed a personal history of gastrointestinal (GI) symptoms including nausea without emesis, abdominal pain, and occasional diarrhea without mention of melena or hematochezia during the preceding year. She had no family history of inflammatory bowel disease, hematologic disease or autoimmune disease.

Based on the history of pathergy (skin lesions at sites of trauma), clinical findings, laboratory findings, histopathology, and multiple negative microbiology studies, the dermatology service favored a diagnosis of pyoderma gangrenosum. Recommendations for therapy included discontinuation of further surgical manipulation including avoidance of grafting, and initiation of systemic corticosteroids at 1–2 mg/kg/day. The primary team was also advised to consider further gastrointestinal and hematologic evaluation to assess for a possible underlying etiology of PG. Gradual improvement of her wounds was noted within three days after initiation of therapy helping to further support a diagnosis of PG. Remarkable improvement was noted at week 7 during an outpatient visit

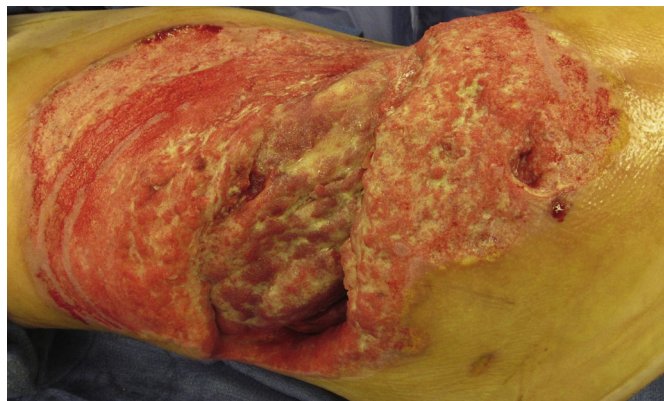


Fig. 2. Extensive deep ulceration from right buttock to flank with exposed subcutaneous fat, fascia, and muscle. Status post serial surgical debridements.

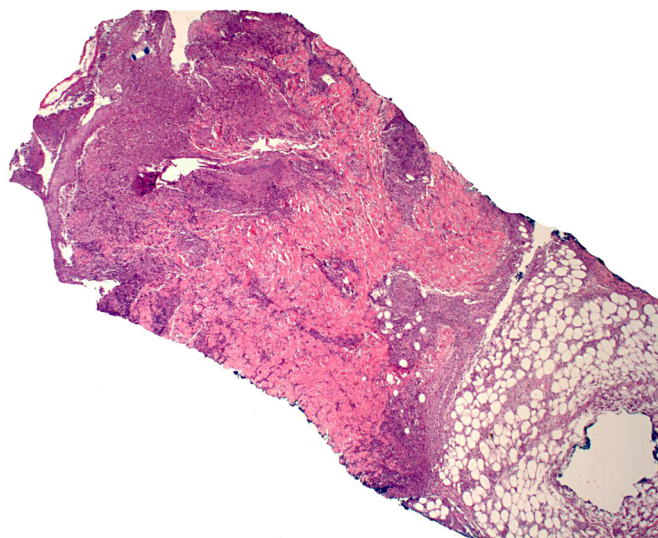


Fig. 3. Nodular and diffuse neutrophilic infiltration of the dermis and subcutis.

(Fig. 4), as well as normalization of her leukocyte count and inflammatory markers.

2. Discussion

Pyoderma gangrenosum (PG) is an inflammatory condition of the skin first described by Brunsting and colleagues in 1930 [1]. The etiopathogenesis of PG is unknown, but studies have suggested that the primary process may arise from abnormal neutrophil chemotaxis as well as impaired phagocytosis and oxygen uptake [2,3]. PG is a neutrophilic dermatosis characterized by recurrent ulcerations or erosions with a peak incidence between ages of 20 and 50 years. There are rare cases of affected children, which comprise 4% of reported cases [4]. Elderly patients are rarely affected and women seem to have higher incidence than men. PG is often associated with systemic disease in about 50% of reported cases, most commonly inflammatory bowel disease (IBD), arthritis, and hematologic disease including acute myeloid and lymphoid leukemia, and monoclonal gammopathy. PG has been described in association with other autoimmune diseases, infections such as the human immunodeficiency virus (HIV), Hodgkin and non-Hodgkin lymphoma and solid tumors [3,5].

Evolution of PG begins as a pustule or vesicopustule that progresses to frank ulceration or deep erosion with violaceous

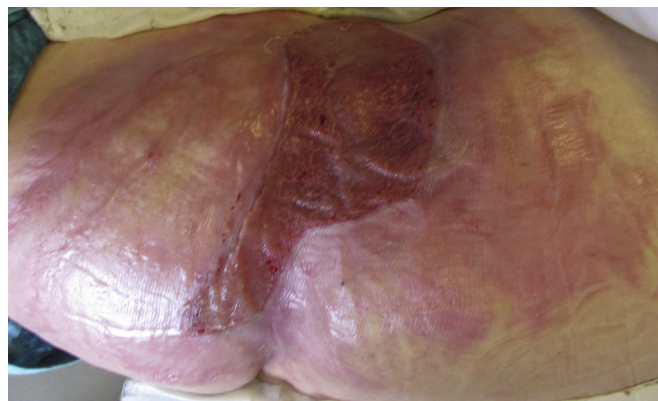


Fig. 4. Significant improvement in ulceration at week 7 of systemic corticosteroid therapy.

overhanging or undermined borders [3,5,6]. There are three major clinically distinct variations. Classic PG, characterized by ulcers usually located on lower extremities in adults whereas in the pediatric population, the buttocks, perineum and head, and neck are most commonly affected; atypical PG characterized by more superficial ulcers or deep erosions with a blue-gray, bullous border found on the hands, arms or face; and peristomal PG, defined by the occurrence of lesions around a stoma, usually following surgery [6]. Prototypic classification of PG includes ulcerative, pustular, bullous, and vegetative types. The course of PG can be acute, relapsing, or chronic. Relapsing or chronic courses are more apt to be associated with an underlying disease process [5,6]. Cutaneous pathergy is an important clinical feature of PG, and is marked by the development of skin lesions as sites of injury [6]. In our patient, ulceration and necrosis developing at the initial site of the gluteal injection, and subsequent ulcers emanating from peripherally inserted central catheter on left upper extremity, coupled with steady enlargement of wounds with each debridement, are all hallmarks of the pathergy phenomenon. Extracutaneous disease is rare, but affects lung (pulmonary infiltrates), bone (“multifocal sterile recurrent osteomyelitis”), and joints (pyoarthrosis). The heart, central nervous system, cornea, liver, spleen, and oropharynx may be involved [6].

Pyoderma gangrenosum is a diagnosis of exclusion and involves elimination of other diseases that cause ulcerative, necrotic or erosive cutaneous lesions [1–7]. The absence of diagnostic laboratory or histopathologic features results in misdiagnosis of PG, estimated at approximately 10% in a retrospective study by Weenig et al. Misdiagnosis exposes patients to risks associated with treatment as seen in our patient. Differential diagnosis of PG includes primary infection such as necrotizing fasciitis, vascular occlusive or venous disease, necrotizing vasculitis, malignant process involving skin and drug-induced or exogenous tissue injury [6,7].

Management of PG depends on severity of the disease and can involve local wound care and topical therapy to use of systemic therapies. Immunosuppressive therapy includes systemic corticosteroids, and steroid sparing agents including tumor necrosis factor inhibitors such as infliximab, azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil, chlorambucil, thalidomide, and other systemic agents [6,7].

In review of the literature, misdiagnosis of PG and treatment as necrotizing fasciitis is not uncommon [3,7–9].

Necrotizing fasciitis (NF) is a severe life-threatening soft tissue infection characterized by rapidly spreading necrosis of the fascia, subcutaneous tissue, muscle and overlying skin [9,10]. It is a rare infectious entity that presents diagnostic and therapeutic challenges for the pediatric surgeon. It has been reported in 0.08/100,000 children/year. Its incidence however, has been increasing in recent years due to invasive *Streptococcus pyogenes*. Initiating factors include minor and major trauma as observed in our patient, surgical wounds and varicella lesions. The most common site of initial involvement in adults is the lower extremity, however, in the pediatric population; it is the abdominal wall, followed by the gluteal region and thigh, head and neck, and upper and lower extremities. Initial skin presentation includes induration or cellulitis with progression to skin discoloration, and bullae formation as observed in our patient. Exquisite pain out of proportion with skin findings, leukocytosis, elevated creatinine kinase, fever, and tachycardia are important associated clinical findings. Presence of ulceration, ecchymosis, crepitus, anesthesia, and necrosis are indicative of an advanced disease process [10]. In a study by Bingol-Kologlu et al., *S. pyogenes* was the most common causative agent in children followed by *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Escherichia coli*, and vibrio species. In contrast to adults, NF is usually a monomicrobial infection in children [10].

NF is common in immunosuppressed and diabetic adult patients. However, it can also affect previously healthy children [11]. Once a diagnosis of NF is suspected, intensive care, early and aggressive surgical debridement followed by appropriate antibiotics is warranted [7–11]. In one large published series, diagnosis of NF was missed in 85–100% of reviewed cases due to the paucity of cutaneous findings early in the course of the disease process [11]. NF is a fulminant infective process, which can result in significant morbidity and mortality. Delayed diagnosis results in a mortality rate of approximately 25–40% [12].

A high index of suspicion is required in the diagnosis of PG or NF. Ulceration, tissue necrosis, and deep erosions are clinical features that can be manifested in both conditions. There is no microscopic pattern that is diagnostic of PG or NF, however, PG usually presents with a predominantly neutrophilic infiltration whereas necrotizing fasciitis has a mixed lymphohistiocytic and neutrophilic infiltrate with suppuration, edema and necrosis of superficial fascia and blood vessel thrombosis in advanced lesions [12]. These findings may be variable depending on biopsy site and the stage of evolution of the lesion. The rapidity of induration and tissue necrosis in hours rather than days may help in defining NF. A positive tissue culture or staining aids in diagnosis of NF, but cannot rule out a secondarily infected PG lesion. Cutaneous pathergy is observed in cases of PG but not in NF. In our case, the lack of clinical improvement with aggressive surgical debridement and systemic antibiotics, multiple negative tissue cultures and stains, histopathologic evidence of neutrophilic infiltration in the dermis and subcutis, evidence of pathergy and eventual improvement with immunosuppression helped in establishing the elusive diagnosis of pyoderma gangrenosum over what was presumed to be necrotizing fasciitis. Our patient still requires further evaluation of her GI symptoms and long-term follow up to rule out an underlying disease process. Aggressive management of PG with systemic antibiotics and extensive surgical debridement can result in large tissue defects with challenging reconstructive implications and psychosocial repercussions. On the contrary, treatment of NF with immunosuppressive therapy may result in significant morbidity and mortality.

3. Conclusion

This case highlights the significance of understanding the etio-pathogenesis, clinical features, and clinical–pathologic correlation in the management of both pyoderma gangrenosum and necrotizing fasciitis. It also illuminates the importance of reconsidering a preliminary diagnosis when a disease process is not responsive to instituted therapy.

Conflict of interest

None of the authors have any relevant financial relationships or conflicts of interest pertaining to this publication.

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